Remarks

Claims 4, 12, 18, and 21 are canceled herein. Claims 1, 5-6, 8, 13-14, 17, and 23-24 are amended herein. Claim 1 is amended herein to incorporate the limitations of claim 4, previous claim 5 and claim 16. Claim 8 is amended herein to incorporate the limitations of claim 12, previous claim 14 and claim 18. Claims 6 and 14 are amended to specify a dose range within the already-examined dose range; the dose range previously recited in claims 6 and 14 is incorporated into amended claims 1 and 8, respectively. Additional support for the amendment of claims 6 and 14 can be found in the specification on page 14, line 20; page 17, line 11-12 and lines 28-29; and page 18, line 7. Claims 5 and 13 are amended to correct dependency. Claims 17 and 23-24 are amended to correct form.

No new matter is added herein. Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks.

Request for an Interview and Interview Summary

The undersigned thanks Examiner Ford for the telephone conference of May 14, 2009, wherein an interview was granted on May 27, 2009. The undersigned thanks Examiners Mondesi and Ford for the interview of May 27, 2009, wherein the submission of an amendment after final action was discussed. If any further is required for entry of this amendment, Examiner Ford is respectfully requested to contact the undersigned at the phone number listed below.

Rejections under 35 U.S.C. § 103 (a)

Claims 1, 4-8, 12-15 and 23-24 remain rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Jahanshai et al., in view of Binder and further in view of Carruthers et al. Claims 4 and 12 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with the rejection as applied to the claims as amended for the reasons of record. Each of the points raised in the Office action are addressed below with regard to the claims as amended.

A) The Office action alleges that the claims are not limited to selecting a subject specifically diagnosed with major depression or dysthymia, since the claims include open transitional claim language "comprising."

The Applicants agree that the claimed methods comprise ("include") the recited steps.

However, the claims are amended herein to clarify that the subject is selected for a disorder **consisting of** major depression or dysthymia, or that the subject is selected for a disorder **consisting of** primary intermittent anxiety and major depression. Janhanshahi et al. teach the selection of subjects with torticollis. These subjects do not have a disorder that consists of major depression or dysthmia, nor do these subject have a disorder that consists of primary intermittent anxiety and major depression.

Jahanshahi et al. teach the use of botullinum toxin to alleviate muscle spasm. The alleviation of muscle spasm and correction of head position results in alleviation of depression. Jahanshahi et al. teach the selection of a subject with torticollis. Thus, the patient population of Jahanshahi et al. simply does not fall within the scope of the patients used in the current method.

Binder et al. suggest the selection of a subject with a headache, and the use of botullinum toxin in these subjects. Binder et al. does not describe subjects with a disorder consisting of major depression or dysthymia.

Carruthers et al. teach selecting a subject for cosmetic use of botullinum toxin.

The selection of a subject with muscle spasm, headache or who desires a cosmetic procedure most certainly does not suggest, nor render obvious, the selection of a subject with a disorder that is only psychological, let alone a subject with a very specific psychological conditions, such as major depression, dysthymia, or primary intermittent anxiety. None of Jahanshahi et al., Binder et al. or Carruthers et al. suggest or provide any motivation to select "a subject diagnosed with a disorder consisting of major depression or dysthymia" or to select a subject that has disorder "consisting of primary intermittent anxiety and major depression," as required in the presently pending claims. In addition, none of the cited references teach the administration of a selective serotonin reuptake inhibitor (SSRI) to these subjects.

The Office action further alleges that it is obvious to combine familiar techniques taught by Jahanshahi et al., Binder et al., and Carruthers et al. However, no teaching or suggestion that a subject be selected based on a psychiatric diagnosis (major depression or dysthymia) as opposed to a physical disorder (torticollis or headache). The proposed combination of references does not yield the claimed invention, hence no *prima facie* case of obviousness has been made.

B) The Office action alleges that since the claims recite "comprising" which is open ended, patients that have other disorders, such as torticollis are not excluded.

As discussed above, the steps of the method comprise ("include") the recited steps. However, the claims as amended herein to clarify that the claimed methods are limited to subjects that have a disorder **consisting of** major depression or dysthymia, or that have a disorder consisting of intermittent anxiety and major depression. As discussed above, the prior art does not suggest the selection of these subject with only specific psychiatric disorders; these subjects are distinct from a subject with a physical disorder, such as torticollis.

C) The Office action states that the Declaration of Dr. Capehart is insufficient to overcome the rejection of claims 1-15, 23 and 24.

The Office action appears to allege that the statements made by Dr. Capehart, who has been established as one of skill in the art, are simply incorrect. The only evidence provided to support the assertion in the Office action that Dr. Capehart et al. is incorrect is the outcome achieved by Jahanshihi et al. As previously discussed, Janhanshai et al. teach that a reduction in muscle spasm in subjects with toriticollis lead to a reduction in their depression. The teachings of Jahanshahi et al. simply do not negate the findings of Dr. Capehart.

In his Declaration, Dr. Capehart confirmed that Jahanshahi et al. does not suggest to a psychiatrist that Botulinum toxin should be used to treat depression in the absence of underlying torticollis. Dr. Capehart provided the information that the innervation of the neck is through the spinal root of the accessory nerve (CN XI) and branches of the second and third cervical nerves (C2 and C3). The corrugator supercilii has innervation from a dual nerve supply with contributions from branches of the frontal, zygomatic and buccal branches of the facial nerve. The procerus has innvervation through the buccal branch of the facial nerve. Thus, given a physician's understanding of anatomy and physiology, a psychiatrist, neurologist or any other physician reading Jahanshahi et al. would not predict that injections of Botulinum toxin into the neck would have the same effect as injection of Botulinum toxin into the corrugator supercilli or procerus muscle, *as the innervation is entirely different*. This Declaration sets forth the scientific basis supporting the assertion that the claimed invention would not be obvious to one of ordinary skill in the art, based on any of the prior art of

record. The Office action simply restates conclusions, and provides no scientific reasoning or basis for the assertions made. The Declaration of Dr. Capehart provides scientific evidence as to why the achieved result was unexpected.

The Office action also states that the Declaration of Dr. Capehart is discounted because the claims are not limited to patients that have only depression. As noted above, the claims are now amended to recite that the subject has a disorder **consisting of** major depression or dysthymia. Applicants respectfully request reconsideration of the Declaration, and the evidence presented therein, with regard to the claims as amended.

D) The Beck Depression Inventory

The Beck Depression Inventory is a well-known method of evaluating clinical criteria. The Applicants do not claim to have invented this Inventory, nor do they dispute that it has value in classifying many types of subjects with psychiatric diorders. Applicants agree that the specification at page 13 confirms that this Inventory can be used to evaluate patient for depression. Thus, it is not surprising that Jahanshahi et al. teach the use of this Inventory.

The ability to diagnose a disease does not render any treatment obvious. For example, if someone is diagnosed with AIDS using a test for the HIV virus, such as a PCR assay, this PCR assay does not render obvious they use of a new treatment with an anti-viral agent. Similarly, any reference to the Beck Depression Inventory as a diagnostic tool does not render obvious the presently claimed methods for treatment.

E) The Declaration of Dr. Finzi

As discussed above, a *prima facie* case of obviousness simply has not been made. In addition, a showing of an unexpectedly superior result overcomes any prima facie case of obviousness.

The claims are limited to methods for treating subjects that have a disorder that consists of only very specific psychological conditions, using the injection of Botulinum toxin into specific muscles, namely the corrugator supercilii or the procerus muscle, and to the use of SSRIs. Dr. Finzi compared the effect of the injection of Botulinum into the different muscles of the face for treating depression. *Results are presented in the specification for three patients; these results were obtained using the*

presently claimed methods in the instant application. These patients diagnosed with major depression or intermittent anxiety/depression, and botulinum toxin was administered to the corrugator supercilii or the procerus muscle of each of these subjects, using the presently claimed methods. The injections treated the depression of all of these subjects, who all reported improvements in their mood. An SSRI was also administered.

Dr. Finzi's Declaration documents that injection of Botulinum toxin into other muscles of the face, such as the lateral orbicularis oculi and the frontalis muscle does not treat depression. Thus, injection of Botulinum toxin into the the corrugator supercilii or the procerus muscle provides an *unexpectedly superior result* for the treatment of depression, as compared to injection of Botulinum toxin into the orbicularis oculi. The unexpected superior results obtained using the claimed methods overcome any prima facie case of obviousness.

Thus, in accordance with MPEP § 2145, the Applicant has provided rebuttal evidence that also includes evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. This is not evidence of secondary considerations, as alleged by the Office action, but rather documentation of the unexpectedly superior results achieved using the claimed methods in human subjects. There is no factual evidence as to why the Declaration has been discounted, only a conclusory statement that "the objective evidence of nonobviousness is insufficient." This is simply an inappropriate standard.

The Applicant has provided a Declaration of one of skill in the art that provides scientific reasoning as to why the claimed methods are unexpected. Moreover, evidence of the unexpectedly superior results achieved with the claimed methods has been provided. In view of the amendments to the claims, the arguments presented herein and in the prior response, and the documentation of the unexpectedly superior results achieved using the claimed methods, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 16-21 remain rejected under 35 U.S.C. 103(a) as allegedly being obvious over Jahanshai et al, in view of Binder, in view of Carruthers et al., and further in view of Wagstaff et al.

The Office action alleges that one of skill in the art would be "motivated to use botulinum toxin to administer SSRIs to treat patients who suffer from depression because Janahanshahi et al has demonstrated that these patients experience psychological aspects such as body concept and low self esteem even after botulinum toxin treatment. Therefore, one of skill in the art would reasonably conclude that the addition of an SSRI such as paroxitine would be effective at treating these patients..." Applicants respectfully disagree.

It is known that many teenagers suffer from psychological disorders such as body concept and low self esteem. However, a psychiatrist would not necessarily treat these conditions with SSRIs. Even if one of skill in the art, such as a psychiatrist, read Wagstaff et al., they would not necessarily administer SSRIs to any subject with an anxiety disorder, low self esteem, or a poor body concept. The Office has simply not provided a motivation or evidence that would lead a psychiatrist to combine Wagstaff et al. with the other references. Indeed, the Declaration of Dr. Capehart describes the medical basis why Jahanshahi et al. does not suggest to a psychiatrist that Botulinum toxin should be used to treat depression in the absence of underlying torticollis. If one of skill in the art would not understand that Botulinum toxin would be of use to treat a subject with a disorder consisting of major depression, dysthmia, or anxiety, then one of skill in the art simply would not be motivated to combine Wagstaff et al. with Jahanshahi et al.

The Applicants further provided a publication, namely Diller et al. that states that that EPS (a syndrome including torticollis) "can and does occur in youth with SSRI. Clinicians should be aware of the SSRIs as a potential causative factor for EPS." *Thus, Diller et al. states that any SSRIs can cause torticollis, this reference is not specific to flouxetine.* However, the Office action discounts Diller et al. by concluding that Diller et al. only teach that fluoxetine and benztropine caused torticollis in a 15-year old. The Office action concludes that since Diller et al. only teach that SSRIs caused torticollis in a youth, but is silent on the effect on other populations, that this reference should be discounted. Applicants respectfully disagree.

The MPEP § 2145states: Office personnel should avoid giving evidence no weight, except in rare circumstances. *Id.* See also *In re Alton*, 76 F.3d 1168, 1174-75, 37 USPQ2d 1578, 1582-83 (Fed. Cir. 1996). In the present case the Office has improperly discounted Diller et al.; the Examiner is

respectively requested to consider Diller et al. in its entirety. Diller et al. teaches one of skill in the art (or perhaps even someone on a medical malpractice jury) to understand that SSRIs can aggravate torticollis. It is not clear why the Office believes that one of skill in the art, reading Diller et al., would understand that SSRIs can induce torticollis in a 15-year old subject, but would not induce torticollis in adults (18+ year old subjects). The Examiner has provided no scientific evidence to support the any difference in effect that SSRIs would have in inducing torticollis in 15 and 18 year olds. The position of the U.S. PTO is completely unsupported by the evidence of record.

Applicants believe that anyone reading Diller et al. would understand that SSRIs could induce torticollis in any subject. Thus, in view of Diller et al., one of skill in the art would most certainly not combine the teachings of Janhanshahi et al. with Wagstaff et al.

Moreover, Dr. Finzi's Declaration further documents that injection of Botulinum toxin into the corrugator supercilii or the procerus muscle provides an *unexpectedly superior result* for the treatment of depression, as compared to injection of Botulinum toxin into the orbicularis oculi. The subject described in the Declaration was being treated with Sertraline (an SSRI). The demonstration of the unexpected superior results obtained using the claimed methods (presented both in the specification and the Declaration) overcomes any *prima facie* case of obviousness.

Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe the present application is ready for allowance, which action is requested. If any matters remain to be discussed before a Notice of Allowance is issued, Examiner is respectfully requested to contact the undersigned for a telephone interview at the telephone number listed below. This is a renewed request for an Interview. In addition, the Applicants respectfully reserve the right to Appeal.

Respectfully submitted,

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